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(54) Title: FLUTAMIDE PREPARATIONS AND METHOD FOR MANUFACTURING THE SAME

(57) Abstract

A pharmaceutical flutamide preparation prepared from a co–pulverized mixture of flutamide with an excipient and a solubilizer exhibits an improved dissolution property of the active ingredient, and thus provides a higher bioavailability of flutamide.

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DESCRIPTION

FLUTAMIDE PREPARATIONS AND METHOD FOR MANUFACTURING THE SAME

TECHNICAL FIELD

The present invention relates to a pharmaceutical preparation comprising flutamide (hereinafter often referred to as "flutamide preparation") as an active ingredient. The present invention also relates to a method for manufacturing the flutamide preparation.

BACKGROUND ART

Flutamide is a generic name for 4'-nitro-3'-trifluoromethylisobutyranilide approved by the United States Adopted Names. Pharmaceutical preparations comprising flutamide as an active ingredient have currently been used for the treatment of prostatic carcinoma. Specific formulations of such pharmaceutical preparations of flutamide are described in, for example, USP 4,474,813.

Flutamide is hydrophobic drug and it is generally considered that flutamide would readily be agglomerated due to the inherent re-agglomerating nature of flutamide and result in a reduction in the dissolution rate of flutamide in the pharmaceutical preparation.

SUMMARY OF THE INVENTION

The present invention provides a novel flutamide pharmaceutical preparation which exhibits the pharmacological effect of flutamide comparable and equivalent to conventional flutamide preparations even though the content of flutamide in the preparation is reduced.

The present invention also provides a method for manufacturing the flutamide pharmaceutical solid preparation exhibiting improvable or comparable bioavailability even with such a reduced content of flutamide.

As a result of extensive studies to achieve the foregoing objects, the present inventors have accomplished the present invention. Thus, the present invention is concerned with the flutamide pharmaceutical preparations and methods for manufacturing the preparations.

Thus the present invention provides pharmaceutical solid preparation comprising flutamide as an active ingredient and having a dissolution property that, when determined according to a paddle method, at least 50% of the flutamide dissolves out from the preparation 30 minutes after initiation of a test according to the paddle method.

The pharmaceutical solid preparation comprises flutamide as an active ingredient together with a pharmaceutically acceptable additive which is preferably

crystalline cellulose.

In a preferred aspect of the present invention, the pharmaceutical solid preparation is obtainable by formulating a co-pulverized mixture of flutamide with an excipient and/or a solubilizer into a pharmaceutical solid preparation.

In a preferred aspect of the pharmaceutical solid preparation of the said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.

The present invention also provide a method for manufacturing a flutamide pharmaceutical preparation which comprises the steps of:

subjecting flutamide and an excipient and/or a solubilizer to co-pulverization using a comminuting machine; and

formulating the resulting co-pulverized mixture into a pharmaceutical solid preparation.

In a preferred aspect of the method of the present invention, said solubilizer has been previously milled using a ball mill, then to the resulting milled powders are added flutamide and the excipient followed by co-pulverization by a comminuting machine and formulation into a pharmaceutical solid preparation.

In another preferred aspect of the method of the present invention, flutamide, the excipient and the solubilizer have been previously mixed with each other,

then the resulting mixture is subjected to co-pulverization by a surface modifying machine followed by formulation into a pharmaceutical solid preparation.

In another preferred aspect of the method of the present invention, said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the results from the dissolution test for the pharmaceutical preparation of the present invention and Odyne® Tablet for comparison.

Fig. 2 shows the results from absorption test for the pharmaceutical preparation of the present invention and Odyne Tablet for comparison when administered into dogs.

Fig. 3 shows the results from absorption test for the pharmaceutical preparation of the present invention and Odyne tablet for comparison when administered into human.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the pharmaceutical solid preparation is in the form of, for example, and not by way of limitation, tablets, capsules, powders, granules, etc. Particularly, the preparation is preferably in the form of tablets.

The solid preparation of the present invention

comprises flutamide as an active ingredient and has a dissolution property that, when determined according to a paddle method, at least 50% of the flutamide dissolves out from the preparation 30 minutes after initiation of a test according to the paddle method.

Preferably at least 60%, more preferably at least 70%, most preferably at least 85% of the flutamide dissolves out from the solid preparation of the present invention 30 minutes after initiation of the test according to the paddle method. In particular, where at least 90% of the flutamide dissolves the solid pharmaceutical preparation of the present invention is most effective as a drug.

The paddle method used herein is, more specifically, Dissolution Test 2 in accordance with the Japanese Pharmacopoeia, 13th revision. The Dissolution Test 2 of the Japanese Pharmacopoeia, 13th revision is specifically defined as follows;

a device used is equipped with a container of 1000 ml volume with a hemispherical bottom, a paddle, a thermostat water bath and a motor;

a rotor of the paddle is designed to have a lower bottom of 42.0 mm with a height of 19.0 $\pm$ 0.5 mm by cutting a disk of 41.5 mm in a radius and 4.0 $\pm$ 1.0 mm in a thickness with a parallel chord, and the upper left and right ends of the rotor have a radius of 1.2 mm;

the rotor with a rotating shaft of 9.4 ± 1.0 mm in a width penetrates through the center of the rotating shaft in such a manner that the lower bottom is at a surface level with the lower end of the rotating shaft on the same surface, to fix vertically with the rotating shaft;

the upper end of the rotating shaft of the paddle is mounted to a supporting shaft designed to rotate together with the motor;

the paddle is dipped in a test solution (1% SDS solution, 900 ml) charged in the container which is previously adjusted to a temperature of 37 ± 0.5°C and rotated at 50 rpm, during which rotation, the rotating shaft is fixed so as to keep a distance of at least 25 ± 2 mm between the lower end of the paddle and the inner bottom of the container; and,

the test is conducted by rotating the paddle at a predetermined position immediately after sinking a specimen (220 mg of the specimen in the case of powders) at the center of the inner bottom of the container, collecting an eluate 30 minutes after and calculating a dissolution rate of the active ingredients from the solid preparation.

In the present invention, the solid preparation may contain the pharmaceutically acceptable additive. Examples of the additive may be an excipient including disintegrators or binders, a solubilizer, a lubricant and other additives that may be conventionally

used in pharmaceutical solid preparations.

In the present invention, excipients conventionally used for solid pharmaceutical preparations may be used without any particular limitation, so long as the excipients can provide the solid pharmaceutical preparation having the dissolution property as defined above. The excipient may also be used in combination of one or more of the other excipient. Typical examples of the excipient include sugars such as glucose, fructose, lactose, anhydrous lactose, sucrose, maltose, mannitol, xylitol, sorbitol, etc.; starch and derivatives thereof such as corn starch, partly pregelatinized starch, potato starch, wheat starch, etc., cellulose derivatives thereof such as crystalline cellulose.

The solid pharmaceutical preparation of the present invention may contain a solubilizer and other additives such as disintegrators, lubricants, binders, etc. that are conventionally used for solid pharmaceutical preparations. Specific examples of the solubilizer are various types of surface active agents such as sodium lauryl sulfate (SDS), sorbitan fatty acid esters, polysorbate, lecithin, etc. In the present invention, it is particularly preferred to use sodium lauryl sulfate. Specific examples of disintegrators include cellulose and derivatives thereof such as crystalline cellulose, low degree substitution hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose; starch and derivatives thereof

such as croscarmellose, hydroxypropyl starch, carmellose, partly pregelatinized starch, etc. Specific examples of binders are crystalline cellulose, methyl cellulose, hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, partly pregelatinized starch, polyvinylpyrrolidone, polyvinyl alcohol, etc. Specific examples of lubricants include magnesium stearate, stearic acid, talc, silica, light anhydrous silicic acid, etc.

In the present invention, the content of flutamide in the solid pharmaceutical preparation is preferably in the range of about 5 to about 80 wt%, more preferably about 20 to about 40 wt%. The content of pharmaceutically acceptable additives in the solid pharmaceutical preparation is preferably in the range of about 20 to about 95 wt%, more preferably about 60 to about 80 wt%.

In a preferred embodiment of the present invention, the pharmaceutical preparation comprises flutamide of about 15 to about 50 wt%, preferably about 20 to about 40 wt% based on the total weight of the preparation, and the balance of pharmaceutically acceptable additives. The pharmaceutical additives are preferably in the range of about 50 to about 85 wt%, more preferably about 60 to about 80 wt% based on the total weight of the preparation. The solubilizer may not always be necessary but optionally and preferably used in the range of about 0.01 to about 50 wt%, more

preferably about 0.1 to about 5 wt% based on the total weight of the preparation.

Generally, flutamide may be administered into a human in a unit dose of 30 to 300 mg.

In the meantime, even if the preparation of the present invention is reduced in the content of flutamide to 30 to 80% of that of the conventional flutamide preparations, the preparation of the present invention can provide a blood level of flutamide equivalent or comparable to that of conventional preparations, when administered into a human. Thus, in the preparation according to the present invention, a unit dose of flutamide may be reduced to 30 to 200 mg, preferably 30 to 100 mg, more preferably 50 to 90 mg.

In a specific embodiment of the present invention, the following components may be exemplified as a unit dosage form for the flutamide preparation.

Components	mg
Flutamide	50 - 180
Crystalline cellulose	40 - 240
SDS	0.1 - 20
Anhydrous lactose	30 - 140
Partly pregelatinized starch	10 - 80
HPC	1 - 20
Carmellose	5 - 80
Lubricant	0.1 - 10

The flutamide preparation of the present invention may be manufactured according to a method which comprises subjecting flutamide together with an excipient or a solubilizer, preferably an excipient and a solubilizer, to co-pulverization and then optionally to granulation into a pharmaceutical preparation. Alternatively, the flutamide preparation of the invention may also be manufactured according to a method which comprises blending flutamide with an excipient and a solubilizer, and subjecting the resulting blend to a heat treatment for thermal granulation into a pharmaceutical preparation. In a preferred embodiment of the present invention, the co-pulverized mixture is mixed with additives necessary for the pharmaceutical preparation, and the resulting mixture is subjected to granulation in a conventional manner. For the granulation, wet granulation, dry granulation and thermal granulation are generally available, but wet granulation is particularly preferred in the present invention.

For the co-pulverization, employed are a ball mill, a speed mill, a pin mill, a hammer mill, a surface modifying machine (HYBRIDIZER, trademark, made by Nara Machinery Co., Ltd., Tokyo) and the like. In particular, it is preferred to use a ball mill and a surface modifying machine. When flutamide together with an excipient are co-pulverized using a ball mill (speed of rotation: 60 rpm, 30-60 minutes), it is preferred that a solubilizer has been previously grinded with the ball

mill (speed of rotation: 60 rpm, 3-10 minutes). Likewise, when flutamide together with an excipient are co-pulverized using a surface modifying machine, it is preferred that flutamide, an excipient and a solubilizer have been previously blended in the machine.

In the co-pulverized mixture, the excipient may be contained in the range of approximately 0.3 to 2.0 parts by weight, preferably 0.6 to 1.2 parts by weight, and the solubilizer is in the range of approximately 0.005 to 0.5 part by weight, preferably 0.01 to 0.3 part by weight, based on 1 part by weight of flutamide. When the co-pulverized mixture is prepared in the present invention, the excipient and the solubilizers as illustrated hereinabove are available. In a preferred embodiment of the present invention, crystalline cellulose and mannitol are employed as the excipient and SDS as the solubilizer, respectively.

A preferred example of the components for the co-pulverized mixture is as follows:

Components	part by weight
Flutamide	60
Crystalline cellulose	48
SDS	1.8

When the mixture having the above components before co-pulverized is subjected to a powder size distribution test as defined in the General Rule for Pharmaceutical Preparations of the Japanese Pharmacopoeia, only 80% or less of the mixture passes through a 48 mesh sieve. However, the mixture after co-pulverized exhibits an improvement that an agglomerating property of flutamide per se has been improved and that the fluidity of flutamide has been also improved. Thus, at least 90% of the co-pulverized mixture, preferably at least 95%, more preferably 97.5% or more, passes through a 48 mesh sieve.

The powder size distribution test as stated above is defined in the Japanese Pharmacopoeia, and the details of the procedure are as follows.

After 10.0 g of a specimen is accurately weighed, the specimen is put on a sieve of 48 mesh. The sieve is covered at the upper aperture. While shaking horizontally for 3 minutes, the sieve is tapped to screen the powders. The screening are then weighed. The inner diameter of the sieve used for this test is set to 75 mm.

Since flutamide is hydrophobic, it is generally considered that flutamide would readily be agglomerated due to the re-agglomerating nature of flutamide itself, which would result in reduction in the dissolution rate of flutamide in the pharmaceutical

preparation. The present invention using the co-pulverized mixture can surprisingly provide the pharmaceutical preparation markedly improved in the dissolution rate of flutamide.

The pharmaceutical preparation of the present invention is orally administered into a human. Flutamide is generally administered at a dose of 125 mg three times per day (Odyne Tablet, 1 tablet) in Japan, and in other countries, flutamide is administered at a dose of 250 mg three times per day. For example, in the United States, two EULEXIN capsules, each containing 125 mg of flutamide, are orally administered three times per day. That is, a daily dose is 375 mg in Japan, and 750 mg in other countries. In the flutamide preparation of the present invention, a unit dose can be reduced to 30 to 80% of the dose for conventional preparations. Even in the such a reduced dose of flutamide, the flutamide preparation of the present invention exhibits a blood level comparable to that of conventional preparations, when administered into a human. Thus, it can be expected that in a less dose, the flutamide preparation of the present invention exhibits the pharamacological and clinical effects equivalent and comparable to that of the conventional pharmaceutical preparations.

The pharmaceutical preparation of the present invention has the dissolution property that flutamide can rapidly dissolve out from the preparation. Therefore, even though the content of flutamide in a unit

dosage is less than conventional flutamide preparations, the blood level of flutamide comparable to that of the conventional preparations can be obtained, when administered into a human. Moreover, differences in the blood level between individuals administered can be minimized according to the flutamide preparation of the present invention.

The present invention is specifically explained with reference to the following examples. Those examples are presented by way of illustration and not by way of limitation.

Example 1

1.8 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 48 g of crystalline cellulose and 60 g of flutamide. The resulting blend was subjected to co-pulverization (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.65 g of anhydrous lactose, 24.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 220 mg in total.

Tablet formulation	Components (mg)
Flutamide	60
Crystalline cellulose	48
SDS	1.8
Anhydrous lactose	56.65
Partly pregelatinized starch	24.3
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 2

2.4 g of SDS has milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 64 g of crystalline cellulose and 80 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting powders were added 45.05 g of anhydrous lactose, 19.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 240 mg in total.

Tablet formulation	Components (mg)
Flutamide	80
Crystalline cellulose	64
SDS	2.4
Anhydrous lactose	45.05
Partly pregelatinized starch	19.3
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 3

1.8 g of SDS, 48 g of crystalline cellulose and 60 g of flutamide were blended followed by co-pulverization (rotation; 4800 rpm, 1 minute) with a surface modifying machine (HYBRIDIZER, trademark, Nara Machinery Co., Ltd., Tokyo). To the resulting powders were added 56.65 g of anhydrous lactose, 24.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 220 mg in total.

Tablet formulation	Components (mg)
Flutamide	60
Crystalline cellulose	48
SDS	1.8
Anhydrous lactose	56.65
Partly pregelatinized starch	24.3
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 4

12.5 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 50 g of crystalline cellulose and 62.5 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.5 g of anhydrous lactose, 24.25 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

Tablet formulation	Components (mg)
Flutamide	62.5
Crystalline cellulose	50
SDS	12.5
Anhydrous lactose	56.5
Partly pregelatinized starch	24.25
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 5

62.5 g of crystalline cellulose and 62.5 g of flutamide were blended in a ball mill followed by co-pulverization (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.5 g of anhydrous lactose, 24.25 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

Tablet formulation	Components (mg)
Flutamide	62.5
Crystalline cellulose	62.5
Anhydrous lactose	56.5
Partly pregelatinized starch	24.25
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 6

6.25 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 56.25 g of crystalline cellulose and 62.5 g of flutamide, and resulting the blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.5 g of anhydrous lactose, 24.25 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

Tablet formulation	Components (mg)
Flutamide	62.5
Crystalline cellulose	56.25
SDS	6.25
Anhydrous lactose	56.5
Partly pregelatinized starch	24.25
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 7

1.9 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 37.1 g of crystalline cellulose and 60 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 28.1 g of anhydrous lactose, 38.2 g of corn starch and 5 g of partly pregelatinized starch. The resulting mixture was subjected to wet granulation followed by size reduction. After mixing further with 0.7 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 171 mg in total.

Tablet formulation	Components (mg)
Flutamide	60
Crystalline cellulose	37.1
SDS	1.9
Anhydrous lactose	28.1
Corn starch	38.2
Partly pregelatinized starch	5
Magnesium stearate	0.7

Example 8

2 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 48 g of crystalline cellulose and 60 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 28 g of anhydrous lactose, 13 g of partly pregelatinized starch, 3 g of HPC and 20 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 175 mg in total.

Tablet formulation	Components (mg)
Flutamide	60
Crystalline cellulose	48
SDS	2
Anhydrous lactose	28
Partly pregelatinized starch	13
HPC	3
Carmellose	20
Magnesium stearate	1

Example 9

1.8 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 48 g of mannitol and 60 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.65 g of anhydrous lactose, 24.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 220 mg in total.

Tablet formulation	Components (mg)
Flutamide	60
Mannitol	48
SDS	1.8
Anhydrous lactose	56.65
Partly pregelatinized starch	24.3
HPC	5
Carmellose	23.25
Magnesium stearate	1

Example 10

62.5 g of flutamide, 92 g of anhydrous lactose, 20 g of polyethylene glycol 4000, 20 g of SDS and 140 g of croscarmellose sodium were mixed with each other, and the resulting mixture was subjected to a heat treatment at 65°C for 15 minutes for thermal granulation. After size reduction, 0.5 g of magnesium stearate was added to the granulated product, the resulting blend was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

Tablet formulation	Components (mg)
Flutamide	62.5
Anhydrous lactose	92
Polyethylene glycol 4000	20
SDS	20
Croscarmellose sodium	40
Magnesium stearate	0.5

Example 11

20 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS was added 62.5 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 92 g of anhydrous lactose, 20 g of polyethylene glycol 4000 and 40 g of croscarmellose sodium. The resulting mixture was subjected to a heat treatment at 65°C for 15 minutes for thermal granulation. After size reduction, 0.5 g of magnesium stearate was added to the resulting powders. The resulting blend was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

Tablet formulation	Components (mg)
Flutamide	62.5
Anhydrous lactose	92
Polyethylene glycol 4000	20
SDS	20
Croscarmellose sodium	40
Magnesium stearate	0.5

Example 12

25 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS was added 125 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 285.3 g of a lactose hydrate/crystalline cellulose physical mixture (Microcelac, Meggle GMBH, Wasserburg), 20 g of polyethylene glycol 4000 and 10 g of croscarmellose sodium. The resulting mixture was subjected to a heat treatment at 65°C for 15 minutes for thermal granulation. After size reduction, 2.35 g of light anhydrous silicic acid and 2.35 g of magnesium stearate were added to the powders, the resulting blend was compression-molded with a tableting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

Tablet formulation	Components (mg)
Flutamide	62.5
MICROCELAC	142.65
Polyethylene glycol 4000	10
SDS	12.5
Croscarmellose sodium	5
Light anhydrous silicic acid	1.175
Magnesium stearate	1.175

Next, the dissolution tests and the animal tests for the flutamide preparations of the present invention as obtained in the Examples as stated above, and the results from those tests are described below, as compared to a conventional preparation.

Test 1:

Dissolution test

1. Specimen

Control: Odyne Tablet (flutamide content: 125 mg, Nihon Kayaku K.K.)

Present invention: Tablet of Example 1

2. Method

Using the two specimens as identified above, Dissolution Test 2 (a paddle method) was performed, respectively, according to the following the procedures

as defined in the Japanese Pharmacopoeia, 13th revision. The conditions are set forth in detail hereinabove. The paddle was rotated at 50 rpm, and 900 ml of 1% SDS aqueous solution was employed as a test solution. The dissolution rate was calculated from the amount of flutamide dissolved out, according to the following equation.

Dissolution rate (%)
= (amount of flutamide dissolved out)/(amount of flutamide originally contained in a specimen) x 100

3. Results

The results are shown in Fig. 1. As is evident from Fig. 1, the dissolution rate of the flutamide for the preparation of the present invention is markedly more rapid than that of the conventional preparation.

Test 2:

Animal test

1. Specimen

Control: Odyne Tablet (flutamide content: 125 mg, Nihon Kayaku K.K.)

Present invention: Tablet of Example 1

2. Method

Each of the tablets together with 50 ml of

water were orally administered into nine (9) beagles previously fasted for at least 18 hours prior to the administration. With passage of time, 5 ml each of blood was collected from beagles through the fore-limb vein. Plasma was sampled from the collected blood, and the metabolite of flutamide, i.e., 2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide (OH-flutamide), was measured by a high performance liquid chromatography.

3. Results

The results are shown in Fig. 2. The area under the plasma concentration-time curve (AUC), and the maximum blood level (Cmax) are also shown in Tables 1 and 2, respectively.

Table 1: Area under the plasma concentration-time curve (AUC)

	mean ± SD	Maximum	Minimum
Odyne Tablet	34.96 ± 12.24	53.48	17.45
Tablet of Example 1	32.26 ± 4.0	38.22	26.23

Tablet 2: Maximum blood level (Cmax)

	mean ± SD	Maximum	Minimum
Odyne tablet	2.63 ± 0.7	3.61	1.43
Tablet of Example 1	2.54 ± 0.23	2.98	2.25

As is well noted from the results in Tables 1 and 2, the kinesis in blood of flutamide after the administration of the preparation of the present invention was substantially equivalent and comparable to that of the conventional flutamide preparation. It was also established that differences in AUC between individuals administered were less reduced in the flutamide preparation of the invention than in the conventional preparation. Those results reveal that the flutamide preparation of the present invention can provide bioavailability of flutamide substantially equivalent that of Odyne tablet containing 125 mg of flutamide, even though the flutamide content in the preparation of the invention is almost half of the content in Odyne Tablet. In addition, the flutamide preparation of the invention can minimize differences in bioavailability between individuals administered of flutamide.

Test 3:

Clinical trials of the flutamide preparation of the present invention

1. Specimen

Control: Odyne Tablet (flutamide content: 125 mg, Nihon Kayaku K.K.)

Present invention: Tablets of Examples 1 and 2 (flutamide contents: 60 mg and 80 mg)

2. Method

Each of the tablets together with 100 ml of water were orally administered to nine (9) normal male adult volunteers previously fasted for at least 12 hours before administration. With passage of time, 7 ml each of blood was collected from volunteers. Plasma was sampled from the blood, and the metabolite, OH-flutamide, was measured by a high performance liquid chromatography.

3. Results

The change in the level of the metabolite in plasma is shown in Fig. 3. The obtained AUC and Cmax are also shown in Table 3.

Table 3

	Area under the plasma concentration-time curve concentration (AUC)	Maximum blood (Cmax)
Odyne tablet	1705.5 ± 625.4	300.3 ± 104.6
Tablet of Example 1 (60 mg)	1400.9 ± 357.9	305.5 ± 58.8
Tablet of Example 2 (80 mg)	1932.8 ± 483.0	396.2 ± 113.0

The results in Table 3 reveal that the blood kinesis of flutamide after the administration of the preparation of the invention was substantially comparable to that of the control group. It was thus established that the flutamide preparation of the present invention exhibits the bioavailability of flutamide substantially the equivalent to or even better than that of the comparative preparation, even if the content of flutamide is reduced.

Industrial Applicability

The flutamide preparation of the present invention has an improved dissolution property and improved absorption of flutamide. Thus, the pharmaceutical preparation of the invention can provide a higher bioavailability with a less flutamide content.

CLAIMS

1. A pharmaceutical solid preparation comprising flutamide as an active ingredient and having a dissolution property that, when determined according to a paddle method, at least 50% of the flutamide dissolves out from the preparation 30 minutes after initiation of a test according to the paddle method.

2. The pharmaceutical solid preparation according to claim 1, wherein at least 75% of the flutamide dissolves out from the preparation.

3. The pharmaceutical solid preparation according to claim 1, wherein at least 85% of the flutamide dissolves out from the preparation.

4. The pharmaceutical solid preparation according to any one of claims 1 to 3, comprising flutamide as an active ingredient together with a pharmaceutically acceptable additive.

5. The pharmaceutical solid preparation according to claim 4, wherein said pharmaceutically acceptable additive is crystalline cellulose.

6. The pharmaceutical solid preparation according to any one of claims 1 to 5, wherein flutamide is contained in the preparation in the range of 30 to 200 mg per unit dosage form.

7. The pharmaceutical solid preparation according to any one of claims 1 to 5, wherein flutamide is in the range of 50 to 90 mg per unit dosage form.

8. The pharmaceutical solid preparation according to any one of claims 1 to 7, which is in the form of a tablet.

9. The pharmaceutical solid preparation according to claim 4, which comprises flutamide of 20 to 40 wt% based on the total weight of the preparation and the balance of pharmaceutically acceptable additives.

10. The pharmaceutical solid preparation according to claim 1, which is obtainable by formulating a co-pulverized mixture of flutamide with an excipient and/or a solubilizer into a pharmaceutical solid preparation.

11. The pharmaceutical solid preparation according to claim 10, wherein at least 90% of the co-pulverized mixture passes through a sieve of 48 mesh, as determined according to a powder size distribution test for a powdery preparation.

12. The pharmaceutical solid preparation according to claim 10, wherein said co-pulverized mixture and said solubilizer are contained in the range of 0.3 to 2.0 parts by weight and 0.005 to 0.5 part by weight, respectively, per part by weight of flutamide.

13. The pharmaceutical solid preparation according to any one of claims 1 to 12, wherein said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.

14. A method for manufacturing a flutamide pharmaceutical preparation which comprises the steps of:

subjecting flutamide and an excipient and/or a

solubilizer to co-pulverization using a communiting machine; and

formulating the co-pulverized mixture into a pharmaceutical solid preparation.

15. The method according to claim 14, wherein said co-pulverization is carried out using a ball mill.

16. The method according to claim 14, wherein said co-pulverization is carried out using a surface modifying machine.

17. The method according to claim 14, wherein said solubilizer has been previously milled using a ball mill, then to the resulting milled powders are added flutamide and the excipient, followed by co-pulverization by a communiting machine and formulation into a pharmaceutical solid preparation.

18. The method according to claim 14, wherein flutamide, the excipient and the solubilizer have been mixed with each other, then the resulting mixture is subjected to co-pulverization by a surface modifying machine followed by formulation into a pharmaceutical solid preparation.

19. The method according to any one of claims 14 to 18, wherein said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.

FIG.1

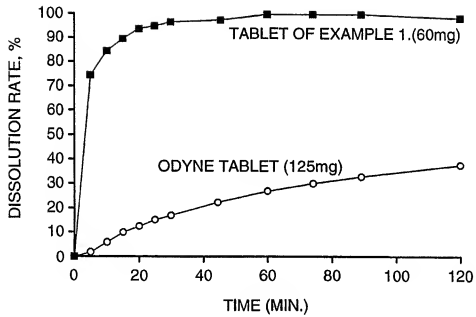

DISSOLUTION RATE, %
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
TIME (MIN.)
TABLET OF EXAMPLE 1.(60mg)
ODYNE TABLET (125mg)

FIG.2

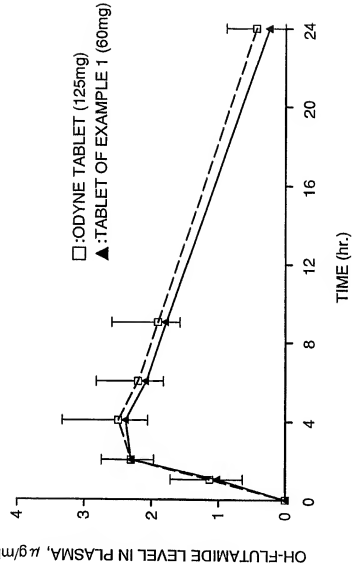
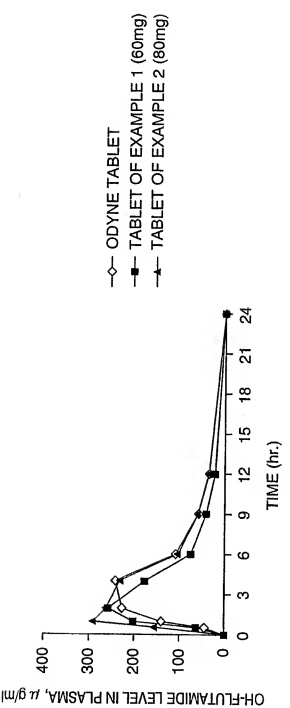

□:ODYNE TABLET (125mg)
▲:TABLET OF EXAMPLE 1 (60mg)
OH-FLUTAMIDE LEVEL IN PLASMA, μg/ml
TIME (hr.)
0
1
2
3
4
0
4
8
12
16
20
24

FIG.3


ODYNE TABLET
TABLET OF EXAMPLE 1 (60mg)
TABLET OF EXAMPLE 2 (80mg)
OH-FLUTAMIDE LEVEL IN PLASMA, μ g/ml
400
300
200
100
0
0
3
6
9
12
15
18
21
24
TIME (hr.)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/JP 98/01769

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/165 A61K9/14 A61K9/20

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	ADEL M S ET AL: "IN VITRO EVALUATION OF FLUTAMIDE-CARRIER SYSTEMS. PART 2: Preparation and evaluation of flutamide systems with alpha-cyclodextrin and beta-cyclodextrin " PHARMAZIE, vol. 52, no. 6, June 1997, pages 470-472, XP000691086 see abstract see figure 4 see page 472, column 2, paragraph 3.2.5	1,2,4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
18 June 1998	02/07/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	La Gaetana, R

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/JP 98/01769

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 474 813 A (NERI RUDOLPH O ET AL) 2 October 1984 cited in the application see abstract see column 1, line 67 - column 2, line 2 see column 2, line 14-20 see column 2, line 25-35 see claims 1,3 ---	1,4-6,8, 9,13
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/JP 98/01769

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